Time to eradicate HTLV-1: an open letter to WHO

Human T-cell leukaemia virus 1 (HTLV-1) is the most potent carcinogenic oncovirus and potentially the most oncogenic risk factor including chemical carcinogens.[1] A unique and aggressive T-cell leukaemia (adult T-cell leukemia) was discovered in Japan,[2,3] from which a new retrovirus, HTLV-1, was identified in the USA[4] and then in Japan,[5] independently. In addition to adult T-cell leukaemia, HTLV-1 causes progressive and disabling inflammatory conditions, such as HTLV-1-associated myelopathy/tropical spastic paraparesis[6,7] (HAM/TSP), associated with high morbidity and mortality. Although not as acute or severe as HIV, HTLV-1, like HIV, produces immune suppression, which leads to opportunistic infections and causes high mortality, a new challenge to public health, particularly in central Australia. In the 38 years since the discovery of HTLV-1, the first human retrovirus (transmitted just like the later-found human retrovirus HIV-1), effective intervention strategies have not been actively publicised. Therefore, HTLV-1 remains a strong threat to individual and community health, and even more so to global health because of the accelerated rate of human migration in recent times.

Additionally, the financial support for HTLV-1 research has been declining in the USA and European countries. We feel strongly that research on the pathogenesis and treatment of this virus needs to be encouraged not only for the sake of HTLV-1 positive patients but also as a model for other human diseases including virus-related cancer. Research into the pathogenesis and development of effective treatments together with the implementation of known preventive strategies on a global scale will be the key drivers of HTLV-1 eradication.

Unfortunately, it has been hard to shift the commonly held belief that we cannot cure HTLV-1 and that therefore there is nothing that can be done. We cannot cure HIV-1 infection either, but thanks to global investment and proactive public health interventions, health-care providers and patients feel equipped and empowered in their fight against HIV-1. The same approach needs to be applied to HTLV-1, which is horizontally transmitted through close contact with fresh blood and unprotected sex, as well as vertically through breast feeding.[8] Reports have highlighted ongoing sexual transmission of HTLV-1 in central Australia,[9] Japan[10] and South America.[11,12] To date, an astounding 17 different prevention strategies have been used widely to reduce the transmission of other blood-borne and sexually transmittable viruses, such as hepatitis B, hepatitis C, and HIV, but not for HTLV-1. Why not?

Preventive measures for HTLV-1 infection through blood transfusion and organ transplantation, such as screening of donated blood products, have been implemented only in some, but not many, countries in which HTLV-1 is endemic, such as parts of Africa, broadly through the Caribbean, Iran, and Australia among Indigenous people. Moreover, the systemic screening of donated organs to exclude the transplantation of positive organs is still a neglected issue worldwide.[13] Japan's Nagasaki Prefecture introduced routine HTLV-1 antenatal screening and formula feeding of babies of HTLV-1-positive mothers in 1987, resulting in a remarkable reduction of the prevalence of HTLV-1 infection from 7·2% to 1·0%.[14] But, so far, this successful prevention of mother-to-child HTLV-1 transmission has been rolled out nationwide in Japan only.

To raise awareness about HTLV-1 internationally, it is imperative to unite isolated patients with HTLV-1, researchers, and health-care providers worldwide. Although the Global Virus Network's HTLV-1 Task-Force, HAM-net (Japan), and HTLV Aware (UK) have been facilitating HTLV-1 education, research, and information, more needs to be done to reach patients globally in an equitable way. Patients positive for HTLV-1, their advocates, scientists, and clinicians have endorsed our open letter to WHO Director-General Dr Tedros Adhanom Ghebreyesus, proposing a collaboration to inform patients and their health-care professionals about effective ways of preventing HTLV-1 transmission.

We have published an open letter[15] to WHO, proposing a WHO HTLV-1 vision for the prevention of HTLV-1 transmission, signed by more than 50 individuals and organisations. The letter states, "it is time to do more for HTLV-1, including five intervention strategies to reduce the incidence of HTLV-1 infection", and we encourage you to read it online.

We declare no competing interests.

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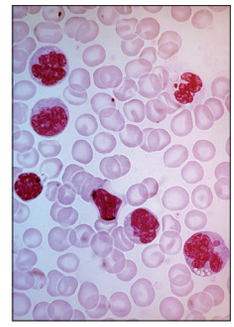

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For more on the **Global Virus Network** see http://gvn.org/

For more on **HAM-net** see http://hamtsp-net.com/english/index.html

For more on **HTLV Aware** see www.htlvaware.com

Submissions should be made via our electronic submission system at http://ees.elsevier.com/thelancet/

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Drawing conclusions from the VIVA trial

The VIVA trial by Jes Lindholt and Rikke Søgaard (Nov 18, 2017, p 2256)[1] assessed the effects of screening for abdominal aortic aneurysm, peripheral arterial disease, and hypertension, showing a small but statistically significant reduction in total mortality in the screening group versus the non-screening group. The authors concluded that "the observed reduction of mortality risk from abdominal aortic aneurysm, peripheral arterial disease, and hypertension" should lead policy makers to "consider implementing combined screening".

However, according to the study's supplementary appendix,[1] there was no effect on any type of cause-specific mortality. The apparent effect on total mortality was small (absolute risk reduction 0·006 [95% CI 0·001–0·011], with 149 fewer deaths in the screening group than in the non-screening group [of >25 000 participants and >2500 deaths in each group]) and was evenly distributed between different causes of death, with no predominance among those causes targeted by the intervention (ie, cardiovascular disease or abdominal aortic aneurysm). The reduction in cancer-related mortalities (33 fewer deaths) contributed twice as much to the difference in total mortality as the reduction in abdominal aortic aneurysm-related deaths (15 fewer deaths). The hazard ratios for mortalities related to cardiovascular disease, other causes, and unknown causes were 0·93, 0·93, and 0·87, respectively (all non-significant).[1] Results were reported after a median follow-up of 4·4 years (IQR 3·9–4·8),[1] with pre-specified follow-up after 3, 5, and 10 years.[2] The mechanism behind the observed difference in total mortality seems elusive, and the risk of a so-called random high should be considered.

Ten randomised trials have assessed the effects of regular health checks targeting cardiovascular disease.[3,4] These trials included more than 200 000 asymptomatic participants and 15 000 deaths, and showed no effects on total or cardiovascular disease-related mortality. The results of the VIVA trial do not change this conclusion.

We declare no competing interests.

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Authors' reply

In their letter, Karsten Juhl Jørgensen and Minna Johansson highlighted the fact that the VIVA trial[1] showed a reduction in overall mortality that could not be attributed to individual causes of death. They further made the case that this overall effect on mortality is inconsistent with current evidence on the effects of general health checks.

We agree that the effect seems diffuse. However, the trial design was never intended to elucidate specific causes of death but instead to test an intervention—combined screening for abdominal aortic aneurysm, peripheral arterial disease, and hypertension, and subsequent appropriate prophylactic treatment—that we believed could be a cost-effective strategy to increase life expectancy in the general population. The alternative strategy of doing separate trials for single screening tests would require far larger sample sizes, and the interpretation would still be affected by the complex interactions of individual cardiovascular diseases (eg, prevention of one such disease could affect the prevalence and prognosis of another or even affect non-cardiovascular diseases such as cancer) and by uncertainty about causes of death. Additionally, because of this complex inter-relatedness of different diseases, health policy makers would not be able to predict the effect of a combined screening programme.

We disagree that the intervention assessed in the VIVA trial should be interpreted under the definition of general health checks—especially those of the past millennium, when modern prophylactic pharmacological management was not yet fully recognised. The review of these older studies mixes primary and secondary prevention.[2] By contrast, the VIVA trial targeted subclinical disease and offered systematic intervention, taking advantage of modern pharmacological agents. Collectively, this screening and treatment resulted in a 7% relative reduction in overall mortality after